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(54) PRODUCTION OF PERMSELECTIVE HOLLOW FIBER MEMBRANES

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain permselective hollow fiber membranes enhanced in membrane strength while holding the membrane capacity thereof and reduced in the leak generation rate thereof.

SOLUTION: A spinning dope soln. obtained by dissolving a cellulose deriv. in a cellulose deriv. soluble org. solvent soln. containing 0-50 wt.% of a polyhydric alcohol is discharged from a tube-in orifice like nozzle by using an aq. soln. containing 0-5 wt.% of the polyhydric alcohol and the above- mentioned org. solvent in total to be passed through air for 0.01-0.3 sec to be immersed in a coagulation soln.

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CLAIMS

[Claim(s)]

[Claim 1] polyhydric alcohol -- 0 - 50wt% -- the spinning undiluted solution which dissolved the cellulosic in the cellulosic solubility organic solvent solution to contain -- polyhydric alcohol and the above-mentioned organic solvent -- the sum total -- 0 - 5wt% -- the manufacture approach of the permselectivity hollow filament characterize by make coagulation liquid immerse after make it breathe out from a tube in orifice-like nozzle and pass the inside of a gas for 0.01 - 0.3 seconds, use the water solution to contain as a heart agent.

[Claim 2] The manufacture approach of the permselectivity hollow filament according to claim 1 characterized by the concentration of the polyhydric alcohol in this organic solvent solution being 15wt (s)% - 35wt%.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention relates to the manufacture approach of a permselectivity hollow fiber useful to especially blood purification. for example, the crown represented by the artificial dialysis film for renal failure patients, especially the beta 2-microglobulin (beta2-MG) which attracts attention by relation with a dialysis patient's long-term complication recently -- it is related with the manufacture approach of a hollow fiber of being suitable for removal of the molecular weight matter. Moreover, it is related with the manufacture approach of a hollow fiber that it is only suitable also for hemofiltration dialysis and hemofiltration.

[0002]

[Description of the Prior Art] the matter of the molecular weight 20,000-40,000 considered to be involved in beta2-MG (molecular weight 11,800) considered to be the causative agent of dialysis amyloidosis, a feeling of itching, the parathyroid hormone (molecular weight 9,500 [about]) considered to be related to hyperlipidemia, the arthralgia, and the ostealgia in relation to a dialysis patient's long-term complication in recent years etc. -- comparatively -- the crown -- the need for removal of the harmful matter of a molecular weight field is cried for. On the other hand, loss of albumin (molecular weight 66,000) indispensable on the body must be avoided as much as possible.

[0003] That is, it excels in the permeability of the with a molecular weight of four to 50,000 or less matter, and, on the other hand, good permselective membrane of the Sharp cut nature of the good cut off molecular weight of the inhibition nature of the with a molecular weight of 60,000 or more matter is desired.

[0004] Although development of the hollow fiber which uses a cellulosic as a raw material from the former has been performed actively As a heart agent when carrying out wet spinning of the hollow filament so that the Japanese Patent Publication No. No. 24165 [58 to] official report may see For example, a liquid paraffin, In order to use what does not have freezing characteristic to a triacetate spinning undiluted solution, such as higher alcohol and isopropyl myristate, In order to raise the concentration of the triacetate in a spinning undiluted solution, not to obtain a colander, in order to make stringiness at the time of spinning high, and to make the coagulation of a spinning undiluted solution inevitably solidified with coagulation liquid from hollow filament external surface after [from a nozzle] ****, a precise structure layer is formed in hollow filament external surface.

[0005] For these reasons, conventionally, compared with the film of a synthetic polymer, the cellulosic hollow filament had the small consistency difference of a compact layer and a porous layer, and was not able to say it with near and the penetrable ability of the matter being enough to a homogeneity layer as a whole.

[0006] In synthetic macromolecules, such as the poly ape phone, what filled the above-mentioned demand comparatively is obtained so that Japanese Patent Publication No. No. 18695 [two to] and the Japanese Patent Publication No. No. 54373 [five to] official report may see, for example.

[0007] On the other hand, the hollow fiber which raised the permeability of a cellulosic, especially triacetate to the heart agent using N2 gas is indicated by the publication-number No. 970 [eight to] official report.

[0008] According to this, the hemodialysis film which is a with a screen multipliers [of beta2-MG] of

0.2 or more hollow fiber, and is characterized by membranous blood water permeability and the screen multiplier of beta2-MG showing 90% or more compared with the value at the time of hemofiltration initiation even if 4 hours pass after hemofiltration initiation by the ultrafiltration coefficient 10 of pure water - 200 ml/m² and mmHg-hr is obtained.

[0009] However, it is comparatively as low as 10 - 120 ml/m² and mmHg-hr, and the hollow filament of a high ultrafiltration coefficient is difficult to get as the spinning in low polymer concentration is difficult and the ultrafiltration coefficient of water is shown in the example by the spinning method of the triacetate which made the gas the core material currently indicated by this official report, since spinning is difficult. Moreover, since there is no freezing characteristic in a heart agent when using a gas as a heart agent, formation of an inside compact layer is difficult, its consistency difference of a compact layer and a porous layer is small as membrane structure, and the film of two-layer structure like the penetrable outstanding synthetic polymer is not obtained. Therefore, it is difficult to obtain the film which can make removal of the amount matter of macromolecules large while being represented with the long-term complication in hemodialysis by beta2-MG which has been a problem.

[0010] Thus, the film which consists of the cellulosic, especially triacetate which are obtained by the conventional manufacture approach has the indefinite consistency difference of a compact layer and a porous layer as membrane structure, and it was not able to be said that it was enough compared with the film which consists of a synthetic polymer like polysulfone also in permeability and fractionation nature for that reason.

[0011] this invention person on the other hand, by adjusting and carrying out spinning of the time amount which passes after the regurgitation and the inside of a gas for a spinning undiluted solution and a heart agent to specific relation It has the compact layer of the specific voidage of the ultra-thin film for membrane structure in the conventional not the homogeneous film but inside. That the cellulosic permselectivity hollow fiber in which supporters could make it the two-layer structure which is a porous layer, and penetrable ability and the fractionation engine performance were excellent is obtained by the header and JP,10-85569,A polyhydric alcohol -- 0 - 50wt% -- in the cellulosic solubility organic solvent solution to contain The water solution to contain is used as a heart agent. the spinning undiluted solution which dissolved the cellulosic -- polyhydric alcohol and the above-mentioned organic solvent -- the sum total -- 5 - 30wt% -- As a typical thing of the hollow fiber obtained by making it breathe out from a tube in orifice-like nozzle, and making the post-coagulation liquid which passed the inside of a gas for 0.006 - 1.2 seconds immersed 30-60 micrometers and a void content 60 - 90%, [a bore] [100-300 micrometers and thickness] The ultrafiltration coefficient (UFR) of pure water 200 - 800 ml/m² and mmHg-hr, And the screen multiplier (SCbeta2MG) of beta2-MG is [the screen multiplier (SCAlb.) of albumin] 0.02 or less further or more in 0.6, and it is indicating that the permselectivity hollow filament that there are few amounts of loss of albumin is obtained.

[0012] However, although this hollow fiber shows sufficient membranous ability, membranous reinforcement is not necessarily enough, and the case where generating of leak is accepted by the spinning approach is accepted.

[0013]

[Problem(s) to be Solved by the Invention] This invention aims at offering the manufacture approach of obtaining a permselectivity hollow fiber with few leak incidence rates, raising membranous reinforcement holding the membranous ability of hollow fibers, such as the conventional UFR and SC.

[0014]

[Means for Solving the Problem] As a result of inquiring wholeheartedly to this technical problem, this invention person lowered further the organic solvent concentration in the conventional organic solvent content water solution for the heart agent, and reached a header and this invention in the range where the gaseous-phase pass time after the cap regurgitation and heart agent concentration are proper.

[0015] namely, this invention -- polyhydric alcohol -- 0 - 50wt% -- in the cellulosic solubility organic solvent solution to contain The water solution to contain is used as a heart agent. the spinning undiluted solution which dissolved the cellulosic -- polyhydric alcohol and the above-mentioned organic solvent -- the sum total -- 0 - 5wt% -- After making it breathe out from a tube in orifice-like nozzle and passing the inside of a gas for 0.01 - 0.3 seconds, the manufacture approach of the permselectivity hollow filament characterized by making coagulation liquid immersed is offered.

[0016] Moreover, this invention offers the manufacture approach of the permselectivity hollow filament characterized by the concentration of the polyhydric alcohol in this organic solvent solution being 15wt(s)% - 35wt%.

[0017]

[Embodiment of the Invention] The structure of the membranous wall of the hollow fiber obtained by the manufacture approach of this invention has the ultra-thin compact layer which determines the separation transparency property of the matter as an inside, it has the supporters who share a membranous mechanical characteristic with the outside, and these supporters have two-layer or multilayer structure which is transparency resistance of the quality of an object and which is the porous layer which is not *****.

[0018] Hereafter, this invention is further explained to a detail. The material which forms the hollow fiber in this invention is a cellulosic, and is especially an acetyl cellulose. Also in it, as what is generally used, it is the polymer which consists of cellulose diacetate and cellulose triacetate substantially, and especially cellulose triacetate is desirable.

[0019] In addition, it means that other amount matter of macromolecules and additives may be contained in the range which does not spoil the property of this cellulosic as it is substantial.

[0020] The solvent which can be used for the hollow filament spinning undiluted solution of this invention is a cellulosic solubility organic solvent, and this is also a water miscibility further. Specifically, N-methyl pyrrolidone, dimethylformamide, dimethyl sulfoxide, a dimethyl amide, dimethylacetamide, etc. are mentioned. It is N-methyl pyrrolidone especially preferably.

[0021] Moreover, the polyhydric alcohol which can be mixed to this organic solvent acts as nonsolvent of a cellulosic. As this polyhydric alcohol, propylene glycol, ethylene glycol, triethylene glycol, a polyethylene glycol, etc. are mentioned, and it is propylene glycol especially preferably.

[0022] As combination of this organic solvent and polyhydric alcohol, it is the combination of N-methyl pyrrolidone and propylene glycol preferably.

[0023] Although especially the cellulosic concentration in a spinning undiluted solution is not limited, it is usually 5 - 18wt%, and is 10 - 15wt% preferably. If 18wt(s)% is exceeded, the inclination in which the porous layer which is supporters carries out eburnation will be shown, and removal engine performance, such as beta2-MG, will fall greatly. If lower than 5wt(s)%, the viscosity of a spinning undiluted solution will become low too much, and silk manufacture will become difficult.

[0024] this organic solvent/polyhydric alcohol in a spinning undiluted solution -- comparatively -- (wt) -- usually -- 100 / 0 - 50/50 -- desirable -- 85 / 15 - 65/35 -- it is 83 / 17 - 75/25 still more preferably.

[0025] this organic solvent and polyhydric alcohol which a heart agent makes form the thin compact layer which was excellent in the inside of a hollow filament at fractionation nature, and were used for the above-mentioned spinning undiluted solution -- the sum total -- 0 - 5wt% -- the water solution to contain is desirable. Since the structure of a compact layer becomes an ununiformity, membranous gas transparency becomes large and leak generating increases it, while the structure of a compact layer will become a non-dense, if it is determined by this organic solvent and polyhydric-alcohol sum density in a heart agent and concentration becomes high.

[0026] Within the limits of this invention, the rate of leak is 5% or less, and when this concentration increases, the rate of leak increases it. At 30%, especially a compact layer also generates the pore which serves as a non-dense further and exceeds the bubbling point. Moreover, if this concentration exceeds 20wt(s)%, the screen multiplier of beta2-MG will become large, and the fall of membraneous ability -- the loss of albumin increases -- is accepted.

[0027] a coagulation bath forms a porous layer by making the outer layer of a hollow filament solidify gently -- it is necessary to make -- therefore, a heart agent -- comparing -- the concentration in the sum total of this organic solvent and polyhydric alcohol (non-solubility) -- 20 - 45wt% -- desirable -- 25 - 40wt% -- it is desirable to make it high. Specifically, the water solution preferably contained by 40 - 60wt% high concentration is desirable 30 - 70wt% in total. If 70wt(s)% is exceeded, coagulation will become slow too much, silk manufacture nature worsens, if lower than 30wt%, a porous layer will serve as an eburnation inclination and removal engine performance, such as beta2-MG, will become low. The hollow fiber obtained by this invention has the compact layer of 30% or less of voidage with a thickness of 2 micrometers or less inside at least.

[0028] In this invention, after making an aforementioned spinning undiluted solution and an aforementioned heart agent breathe out from a nozzle, before making it immerse and solidify to the above-mentioned coagulation liquid, it is the description to pass the zone of the gas between 0.02 seconds - 1.2 seconds.

[0029] The coagulation of the inner layer section of a hollow filament will progress by passing a gas zone earlier than the outer layer section, the thin compact layer which determines the separation permeability of the matter as an inside is formed, the porous layer which turns into supporters who share a membranous mechanical characteristic with the outside is formed, and the hollow filament which has the permselectivity of high performance in this way is obtained.

[0030] If shorter than 0.02 seconds, a compact layer will occur also in an outer layer and the removal engine performance of amount protein of inside macromolecules like beta2-MG will fall to it.

Conversely, if it becomes longer than 1.2 seconds, the eburnation of a inner layer will progress too much, and the film which a compact layer becomes thick too much and has the highly efficient permselectivity currently searched for is not obtained.

[0031] The description of the engine performance of this hollow fiber is the thing of the conventional high level which was not comparatively obtained by the film of homogeneity structure, and the ultrafiltration coefficients of pure water are about 800 ml/m² and mmHg-hr, and DA of a dextran (molecular weight 10,000) is about 70, and it is the hollow fiber in which has good albumin rejection (the screen multiplier of a dextran (molecular weight 70,000) is about 0.2), and penetrable ability and the fractionation engine performance were excellent.

[0032]

[Example] Although an example is given and this invention is explained still more concretely hereafter, this invention is not limited at all by these examples.

[0033] Measurement of the rate of leak is KOSUMO about the pressure drop when having filled up the blood side with air by considering the dialysing fluid side of a hollow fiber dialyzer as disconnection, pressurizing for 15 seconds and holding by 1.0kg/cm². It measured using the air leak circuit tester by the Instrument Co.LTD. company. The pressure drop at that time judged 25 or more mmAqs to be leak.

[0034] Moreover, measurement of DA (dextran MW = 10,000) is performed as follows. While pouring the water solution which dissolved the dextran (molecular weight = 10,000) in RO water by the concentration of 0.2 g/L by part for 200ml/from the blood close side of a hollow fiber dialyzer, RO water is sampled to a dialysing fluid side, and dextran former liquid and the solution from a dialyzer blood appearance side are sampled after a sink and 10 minutes by part for 500ml/. The flow rate by the side of the blood appearance at the time of zero (QB0) and the amount of dialysing fluid appearance side streams (QB0) are measured. Each sampling liquid was made to color with an anthrone sulfuric-acid solution, the absorbance with a wavelength of 620nm was measured, and DA was calculated by the following formula.

The flow rate QB0 by the side of absorbance QBi:dialyzer blood close [of the absorbance CB0:dialyzer blood appearance side solution of $DA = (CBi \times QBi - CB0 \times QB0) / CBi \times CBi$:dextran former liquid]: The flow rate by the side of dialyzer blood appearance [0035] Moreover, SC (dextran MW = 70,000) was measured by the following approaches. Filtrate is made to flow out by part for 10ml/from a dialysing fluid side, adjusting a sink and a pressure loss for the solution which dissolved the dextran (molecular weight 70,000) in RO water by the concentration of 0.2g / L by 200/from an entering [a dialyzer]- blood side. After 10 minutes, from the dextran former liquid and dialysing fluid side, sampled **** respectively, it was made to color with an anthrone sulfuric-acid solution, the absorbance with a wavelength of 620nm was measured with the spectrophotometer, and SC was calculated by the following formula.

$SC = CF / CBi \times CBi$: Absorbance CF of dextran former liquid : Absorbance of dialyzer dialysing fluid side filtrate [0036] Examples 1-2 and the [examples 1-4 of comparison] cellulose triacetate (whenever [acetylation] 60.5, a degree of polymerization 360, Daicel Chemical Industries, Ltd. make) are used as a solvent. N-methyl pyrrolidone (NMP), The spinning undiluted solution which dissolved the propylene glycol (PG) as nonsolvent polyhydric alcohol by the system mixed at a rate given in Table 1 is used. Using the water solution of a presentation of the same Table 1 publication of NMP and PG as a heart agent, from the double pipe nozzle, the regurgitation [the inside of the air of a distance given in Table

1], and after making it pass, introduce into coagulation liquid, and it was made to solidify, rinsed, and scraped off after glycerol adhesion processing. The obtained hollow fiber was inserted in the after [desiccation] tube-like case, adhesion immobilization of the both ends was carried out with polyurethane, and effective area produced the hollow fiber dialyzer of 2 about 1.5m. The screen multiplier SC (DX70,000) of the dextran 70,000 equivalent to DA (DX10,000) and the albumin of a dextran 10,000 which are equivalent to the ultrafiltration coefficient (UFR) of pure water and beta2-MG by in-vitro was measured. A result is shown in Table 1.

[0037]

[Table 1]

項目		実施例 1	実施例 2	比較例 1	比較例 2	比較例 3	比較例 4
紡糸	セロ-アセト (wt%)	1.3	←	←	←	←	←
原液	NMP (wt%)	6.8	←	←	←	←	←
	PG (wt%)	1.9	←	←	←	←	←
芯	NMP (wt%)	0	4	8	12	16	24
剤	PG (wt%)	0	1	2	3	4	6
	水 (wt%)	100	95	90	85	80	70
紡糸ドープ温度	(℃)	60	←	←	←	←	←
紡糸ドラフト		1.3	←	←	←	←	←
凝	NMP (wt%)	3.9	←	←	←	←	←
固	PG (wt%)	1.1	←	←	←	←	←
液	水 (wt%)	5.0	←	←	←	←	←
エアギャップ長	(mm)	5.0	←	←	←	←	←
気相通過時間	(秒)	0.075	←	←	←	←	←
紡速	(m/分)	40	←	←	←	←	←
中	内径 (μm)	200	←	←	←	←	←
空	膜厚 (μm)	3.7	3.7	3.7	3.9	4.0	3.9
糸	UFR (ml/m ² ·mmHg·hr)	760	795	861	910	1025	1152
性	DA (DX10,000)	7.2	7.3	7.5	7.5	7.8	7.4
能	SC (DX70,000)	0.203	0.216	0.236	0.261	0.286	0.318
リーク率		0/9	1/31	1/15	3/28	5/30	5/16
(%)		0	3.2	6.9	10.7	16.6	31.3

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CORRECTION OR AMENDMENT

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[Procedure amendment 1]

[Document to be Amended] Specification

[Item(s) to be Amended] 0028

[Method of Amendment] Modification

[Proposed Amendment]

[0028] In this invention, after making an aforementioned spinning undiluted solution and an aforementioned heart agent breathe out from a nozzle, before making it immerse and solidify to the above-mentioned coagulation liquid, it is the description to pass the zone of the gas between 0.01 seconds - 0.3 seconds.

[Procedure amendment 2]

[Document to be Amended] Specification

[Item(s) to be Amended] 0030

[Method of Amendment] Modification

[Proposed Amendment]

[0030] If shorter than 0.01 seconds, a compact layer will occur also in an outer layer and the removal engine performance of amount protein of inside macromolecules like beta2-MG will fall to it. Conversely, if it becomes longer than 0.3 seconds, the eburnation of a inner layer will progress too

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